Effect of Epinephrine on the Peripheral Metabolism of Thyroxine

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A B S T R A C T   10 normal young men received reposi-
tory epinephrine repeatedly for 4 days during the course
of a radiothyroxine (radio-T4) disappearance curve.
During epinephrine administration, serum radio-T4 dis-
appearance rate (k) slowed abruptly, fecal clearance de-
creased, urinary clearance was initially unchanged but
later decreased slightly, volume of thyroxine distribution
decreased, and external radioactivity over the liver
remained unchanged. Beginning on day 2 of epinephrine
and persisting at least 1 day after epinephrine was dis-
continued, serum thyroxine-binding globulin (TBG)
maximal binding capacity increased, thyroxine-binding
prealbumin (TBPA) maximal binding capacity de-
creased, and free T4 iodine decreased. Stable serum T4
iodine decreased during the experiment. Three indexes,
namely the free T4 iodine, the reciprocal of TBG
capacity, and the urinary radio-T4 "clearance" changed
in parallel, suggesting that the increase in TBG capacity
was responsible for a delayed decrease in radio-T4
metabolism. However, these changes were temporally
dissociated from the decrease in k, which began and
ended abruptly with initiation or discontinuing of
epinephrine administration. This dissociation is unex-
plained, but may be caused by alterations in T4 binding
in tissue sites.

INTRODUCTION

Studies in the rodent (2–4) have suggested that epineph-
rine stimulates degradation of thyroxine (T4). The
present study was undertaken to confirm this finding
in man.

When radiothyroxine (radio-T4) was administered
to normal men and its disappearance rate measured, the
subsequent injection of epinephrine unexpectedly caused
a *decrease* in the T4 disappearance rate. We therefore
examined this phenomenon in detail, measuring serum
protein-bound ^{131}iodine (PB^{131}I) and iodide-^{131}I, urinary
and fecal radioactivity, serum T4–binding proteins,
serum free stable T4 iodine (T4-I) concentration, and
the volume of distribution of the injected T4.

A complex picture unfolded from these studies, as
a result of which it became clear that the free T4 con-
centration could not be the sole determinant of the rate
of T4 disappearance.

METHODS

11 euthyroid young men, paid volunteers, were studied. One
subject was studied for a shorter period, and only his serum
radio-T4 disappearance rate data are included in this report.
The other 10 subjects underwent the following procedure:

(*a*) 50 μc of T4 labeled in the 3', 5' positions with ^{131}I
(radio-T4) (about 40 mc/mg, specific activity) was admin-
istered intravenously at 4 p.m. on day 1. 1 g of carmine was
taken by mouth as a stool marker at this time, and also at
9 a.m. of day 7 and 9 a.m. of day 11 to differentiate stools
formed during the three experimental periods. Stable iodine
as Lugol's Solution was administered immediately (5 drops
every 8 hr for 1 day, then 1 drop every 8 hr for the
remainder of the experiment) in order to block thyroidal
uptake and recirculation of radioiodide resulting from de-
iodination of the radio-T4.

(*b*) Beginning immediately after the radio-T4 injection
and continuing throughout the next 15 days, blood samples
were collected twice daily, at 9 a.m. and 3 p.m., all urine was
collected in 24-hr aliquots, and all stools were saved. All sera
were counted for total radioactivity. In addition, all 3 p.m.
sera were counted after removal of radioiodide by passage
through a short column of Amberlite IRA 400 anion-exchange
resin. (Control studies showed that approximately 10% of
the T4 in the serum is lost by this technique, and approxi-
mately 2% of an iodide standard escapes the resin. As all
sera were treated in an identical manner, intercomparisons

were made without correcting for these factors.) Urines were mixed, measured, and aliquots counted for radioactivity level. Stool specimens were individually homogenized and weighed. Weighed aliquots were counted for ^{131}I level. All of these specimens were counted in duplicate in a well-type scintillation detector, and the counts were compared with a standard made from the same radio-T4 solution as that injected.

In addition, daily external counts of radioactivity over the liver and thigh were made in eight of the subjects, and daily counts over the thyroid and thigh (to check for completeness of the iodine block of thyroid uptake) were made in two subjects. These counts were compared with a dilution of the dose contained in a 25 ml volume in a 50 ml beaker.

(c) After 40 hr had been allowed for distribution of the isotope in its tissue compartments (i.e. at 9 a.m. on day 3 of the experiment), a 4 day precontrol period was begun. During this period the observations outlined above were carried out. Extra sera for binding studies and stable T4-I determination were drawn on the afternoons of the 1st and 4th days of this period.

At 9 a.m. on day 7, the 4 day epinephrine period was begun. On these days, a repository crystalline epinephrine suspension (Susphrine) was given as a subcutaneous dose of 1.5 mg at 9 a.m., 12 noon, 3 p.m., 7 p.m., and 11 p.m. (a total of 7.5 mg daily for 4 days). When residual clinical effects from the preceding dose were still evident at the time a dose was scheduled, doses were reduced, but in all cases at least 6.0 mg of epinephrine was given each day. During this period, observations as above were continued, and daily serum samples for binding studies and stable T4-I determinations were collected.

Days 11–14, the 1st 4 days after epinephrine was discontinued, constituted the 4 day postcontrol period. Observations were made as in the precontrol period.

(d) Sera for studies T4 binding and stable T4 concentration were frozen and saved so that all specimens from a given subject could be studied simultaneously. Stable T4-I determinations were done by the column chromatographic method (5) by Bioscience Laboratories, Van Nuys, Calif. This method measures iodine of both T4 and triiodothyronine (T3).

Dialyzable T4 was measured by an equilibrium dialysis method modified from the methods of Oppenheimer, Squef, Surks, and Hauer (6) and Ingbar, Braverman, Dawber, and Lee (7). Serum was labeled with radio-T4 which had been dialyzed to remove radioiodide (8). 0.2 ml of labeled serum plus 4.8 ml of phosphate buffer (pH 7.4) was dialyzed against 25 ml of the same buffer for 18 hr at 37°C in a shaking incubator (6). The dialysate was then diluted 1:1 with indifferent serum, and any radioiodide contaminating the dialysate was removed by a second dialysis of the serum-diluted dialysate against buffer containing an anion-exchange resin (7). The dialyzable fraction was multiplied by the serum T4 value to obtain the "free T4-I."

Electrophoresis for determination of the distribution and T4 capacity of the T4-binding proteins was done on an agar gel medium on plastic slides in Tris maleate buffer (8). Bands of radioactivity were located by radioautography of the slides after electrophoresis. The gel-coated slides were then cut between the bands of radioactivity. The segments were placed in counting tubes, and the radioactivity levels were quantitated. Stable T4 enrichments of 2 μg/100 ml, 150 μg/100 ml, and 600 μg/100 ml were used, with each serum studied in duplicate at each enrichment level. TBG capacity was measured with 150 μg/100 ml enrichment, while

TBPA capacity was measured using enrichment to 600 μg/100 ml.

T3 resin uptake tests were done with the Abbott Triosorb kit.

Statistical methods used included the least squares method (for calculations of the regression of the logarithm of serum radioactivity with time and its standard error) and Fisher's t test for paired and for unpaired variables (9).

In addition to the average value for the serum disappearance rate (k) derived from the individual regression calculations for each experimental period, a day-by-day estimation of k was made. Because of the relatively large fluctuation in individual serum radioactivity due to random and other unrelated factors, successive 3 p.m. and 9 a.m. serum values were pooled for this purpose. The logarithm of each 3 p.m. serum value was averaged with the logarithm of the following day's 9 a.m. serum value, and the result was taken as the logarithm of the serum "midnight" value. The logarithm of the decrease in serum radioactivity during a given day is then the difference between the "midnight" values beginning that day and ending it. k is the antilogarithm of this difference. Expressed algebraically:

If S_1 = concentration of ^{131}I in the 3 p.m. serum on preceding day;

S_2 = concentration of ^{131}I in the 9 a.m. serum on the day under question;

S_3 = concentration of ^{131}I in the 3 p.m. serum on the day under question;

and S_4 = concentration of ^{131}I in the 9 a.m. serum on the following day; then log $k = \frac{1}{2}(\log S_1 + \log S_2) - \frac{1}{2}(\log S_3 + \log S_4)$.

When the difference between the mean serum k values for successive days was unequivocally random, as judged by
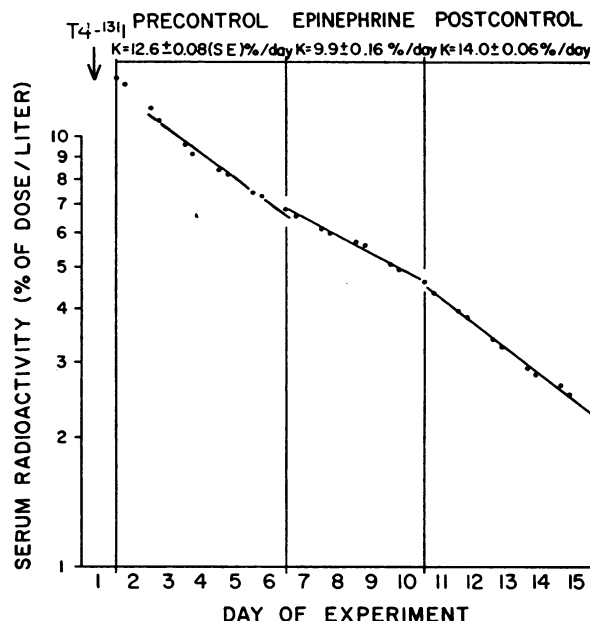

FIGURE 1 Serum radiothyroxine (radio-T4) concentration (logarithmic scale). Lines indicate least squares calculations for the period indicated. Disappearance constant (k) with the standard error of k are calculated from the least squares solutions.

an arbitrary criterion of ($P > 0.30$), each subject's k values for these 2 days were averaged. In these instances, the 2 day mean k values were used in the statistical calculations and graphic presentation rather than daily values, in order to further reduce the influence of random fluctuations in the data.

RESULTS

All subjects tolerated the experiment well. Pulse rates 30 min after a Susphrine injection averaged 20 beats/min above base line measurements, but blood pressure was little affected. Some subjects developed facial pallor which persisted throughout the period of epinephrine administration. During epinephrine administration all subjects complained of shakiness and short temper. These subjective effects, however, diminished markedly on days 3 and 4. No measurements were made of blood volume or kidney function during this experiment.

Serum radio-T4 disappearance. The rate of disappearance of radio-T4 from the serum decreased as soon as epinephrine was begun. Fig. 1 shows the logarithm of the average serum radioactivity levels for 10 subjects (treated as those from an idealized individual), plotted against time. Daily disappearance constant (k) for the three experimental periods, calculated from these data, are indicated. Similar analysis was done of the serum curve from each individual subject, with calculation of k values for the three periods. These k values are shown in Table I. k is significantly greater in the precontrol and postcontrol periods than in the epinephrine period.

Day-by-day k values, calculated as described above, are presented in Fig. 2. For orientation, the k predicted for males of the average age of this group, by the formula of Oddie, Meade, and Fisher (10), is presented as a dashed line. On precontrol days 1 and 2, representing the period from 40 to 88 hr after radio-T4, the day-by-day k remained higher than predicted, whereas on precontrol days 3 and 4 the average day-by-day k compared well with the theoretical value. It then decreased significantly below the base line level early in the epinephrine period with the nadir on epinephrine day 2. On epinephrine days 3 and 4 there was a significant rise toward the base line level, and the values for these days did not differ significantly from those for precontrol days 3 and 4.

During the early postcontrol days, the day-by-day k rose significantly above that of the late epinephrine period and above the base line established on precontrol days 3 and 4. This elevation persisted throughout the 4 day postcontrol period. Observations were actually continued for 2 additional days, permitting calculation of k for postcontrol day 5. At this point in the experiment, count rates were very low, so that random variability in the calculated serum values was great. Nevertheless, as indicated in Fig. 2, on postcontrol day 5 the value of k for serum radio-T4 was near the base line level, and was significantly less than on postcontrol days 3 and 4.

Serum inorganic radioiodine. The ratio of radioactivity in serum after removal of radioiodide by passage

TABLE I

Daily Turnover Rate (k) During the Three Phases of the Experiment

Subject	k				Δk		
	Precontrol	Epinephrine	Postcontrol		Precontrol — epinephrine	Postcontrol — epinephrine	Postcontrol — precontrol
	%/day					%/day	
R. M.	15.4	13.0	14.6		2.4	1.6	−0.8
T. W.	13.9	9.9	16.2		4.0	6.3	2.3
R. W.	12.7	8.3	14.5		4.4	6.2	1.8
R. H.	11.8	6.9	13.2		4.9	6.3	1.4
S. B.	16.3	9.3	14.6		7.0	5.3	−1.7
R. S.	13.6	9.7	16.7		3.9	7.0	3.1
N. S.	10.7	10.6	15.5		0.1	4.9	4.8
N. H.	13.5	9.6	14.3		3.9	4.7	0.8
H. M.	11.7	7.7	9.7		4.0	2.0	−2.0
H. R.	12.3	8.8	13.7		3.5	4.9	1.4
T. H.	14.8	8.8	15.2		6.0	6.4	0.4
Mean	13.3	9.3	14.4	Mean	4.0	5.1	1.1
SD	1.7	1.6	1.9	SE	0.54	0.54	0.61
				t	7.44	9.35	1.72
				P	<0.001	<0.001	NS

Precontrol = 9 a.m. serum on 2nd day after radiothyroxine injection through 9 a.m. serum drawn just before first epinephrine injection; epinephrine = 9 a.m. serum drawn just before first epinephrine injection through 9 a.m. serum drawn the morning after last epinephrine injection; postcontrol = All sera drawn during the 5 days after completion of the epinephrine injections.
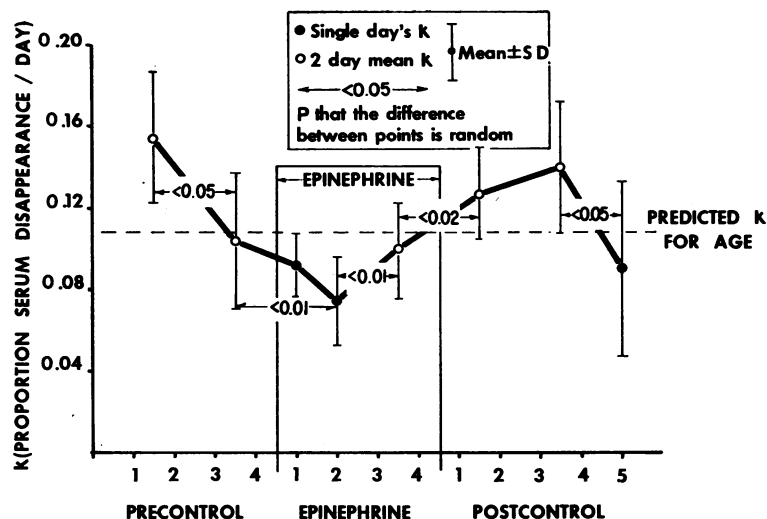
FIGURE 2 Serum "day-by-day k" values. When 2 successive days' values did not differ (P < 0.30), pooled values for the pair of days are shown. Arrows indicate significant differences.

through an anion-exchange resin to that in the untreated serum was 0.90 ±0.06 (SD) during the precontrol period, 0.91 ±0.01 during the epinephrine period, and 0.93 ± 0.08 during the postcontrol period. None of these differences is statistically significant.

Urinary radioiodide. Urinary radioiodine "clearances" are presented in Fig. 3. These were calculated as the ratio of the daily urinary ^{131}I to the ^{131}I present in 1 ml of serum. The serum ^{131}I was predominantly present as T4, and the urinary ^{131}I was predominantly iodide. As thyroid uptake was blocked, and fecal ^{131}I is thought to be predominantly T4 (11), this urinary "clearance" accounts for disposal of almost all of the radioiodide resulting from deiodination of radio-T4. Hence, these "clearance" rates should correspond closely to the actual T4 deiodination rate.

Fig. 3 shows that deiodination rate was initially unaffected by epinephrine administration. On days 3 and 4 of the epinephrine period and persisting 1 day into the postcontrol period, urinary radioiodine "clearance" decreased. This decrease was variable, and is of only borderline significance. The decrease in urinary "clearance" coincided in timing and magnitude with the decrease in serum free T4 to be demonstrated below.

Most subjects showed a distinct peak in the urinary T4 "clearance" on either day 3 or 4 of the postcontrol period of the experiment. The average "clearances" for these 2 days were significantly higher than were the average precontrol "clearances." This peaking occurred at a time when the "day-by-day k" was still elevated, but serum TBG capacity had returned to control levels.

Fecal T4 excretion. Fecal clearances of serum T4 are presented in Table II. These clearances were calcu-

lated in the following way: stools corresponding to the beginning of each experimental period were identified by presence of the carmine marker. Radioactivity in all stools belonging to each experimental period was summed for each subject and expressed as mean fecal excretion per day during the given period. Geometric mean for serum radio-T4 concentration during the experimental period was determined graphically. Clearance in milliliters per day was then calculated from the ratio:

$$\frac{\text{mean fecal } ^{131}\text{I (per cent of dose per day)}}{\text{geometric mean serum } ^{131}\text{I}}.$$

(per cent of dose per milliliter)

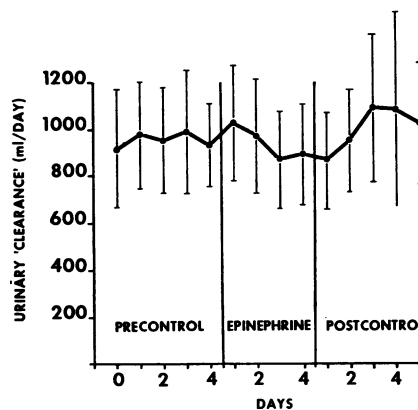Only data for those subjects whose stool collections were believed to be complete are presented. In all cases,

FIGURE 3 Urinary "clearance." Points and vertical lines indicate the mean ± standard deviation for the clearances of individual subjects.

TABLE II
TABLE II

Fecal Clearances During the Three Phases of the Experiment

Subject	Fecal clearance				Δ Clearance		
	Precontrol	Epinephrine	Postcontrol		Precontrol − epinephrine	Postcontrol − epinephrine	Postcontrol − precontrol
	ml/day					*ml/day*	
R. M.	185	152	195		33	43	10
T. W.	302	134	249		168	115	−53
R. H.	147	134	147		13	13	0
S. B.	303	141	—		162	—	—
R. S.	234	233	316		1	83	82
N. S.	269	240	370		29	130	101
N. H.	206	162	—		44	—	—
H. M.	187	119	317		68	198	130
H. R.	247	63	300		184	237	53
Mean	231	153	271	Mean	78	117	46
SD	54	55	78	SE	24	30	24
				t	3.25	3.90	1.92
				P	<0.02	<0.01	NS

fecal excretion of radioactivity was reduced during epinephrine administration, though in some cases this reduction was very small. As indicated in Table II, this decrease is statistically significant.

Volume of distribution. The apparent volume of radio-T4 distribution was calculated as:

$$\frac{100 - (\text{total accumulated per cent of the dose excreted in urine and feces})}{\text{per cent of dose per liter of serum}}.$$

This calculation assumes that there was no thyroidal uptake of radioactivity, and that all loss is accounted for. Mean volumes of distribution with their standard deviations are shown in Fig. 4 as the upper curve of solid circles. It will be seen that this curve has a general slight upward deviation, presumably due to some thyroidal uptake or unmeasured excretion. A regression line calculated from the mean values for each day during the two control periods has the equation: $V = 10.716 + 0.102\,t$, where $V =$ volume of T4 distribution in liters, and $t =$ time in days. The upward slope of this line (0.102 liters/day) represents the average "clearance" into the thyroid or unmeasured excreta (the "U clearance"). This upward slope is, in fact, very small and does not differ significantly from zero statistically; as it seems very unlikely that *no* unmeasured loss occurred, however, we chose to correct for "unmeasured clearance." The hatched line in Fig. 4 indicates volume of distribution when this "U clearance" has been taken into account.

During the period of epinephrine administration, the volume of distribution decreased an average of 740 ml

($P < 0.02$). This decrease can be seen in Fig. 4 and also in Fig. 1, where it appears as a slight discontinuous rise in the position of the regression line of serum ^{131}I for the epinephrine period when compared to either the precontrol or the postcontrol period.

Thyroidal clearance. In two subjects, thyroidal radioactivity was measured by external counting to estimate the efficiency of the iodide block. At the end of 15 days, 2% and 3% of the dose, respectively, had accumulated in the thyroid gland. This represents daily thyroidal "clearances" of 22 ml and 37 ml.
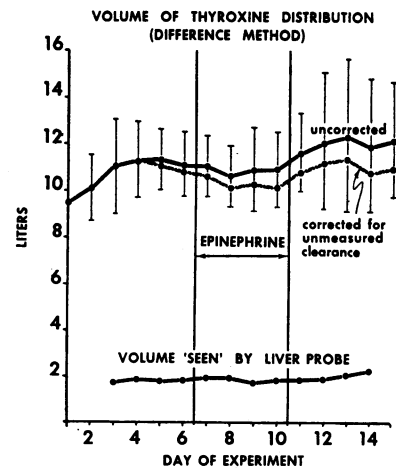

FIGURE 4 Volume of distribution of radio-T4, with and without correction for the unmeasured "U clearance." Volume "seen" by a scintillation detector placed over the area of liver dullness. Points are means of the individual volumes. Vertical lines indicate ±1 SD.

TABLE III
Thyroxine Iodine (By column)

Subject	Precontrol Day.... 1	4	Epinephrine 1	2	3	4	Postcontrol 1	4	Mean difference from mean precontrol Epin. 1 − 2	Epin. 3 − 4	Post-control
	μg/100 ml		μg/100 ml				μg/100 ml		μg/100 ml		
T. W.	3.3	4.9	4.2	3.2	4.0	4.1	3.5	3.9	0.40	0.05	0.40
R. W.	3.9	3.5	3.3	3.8	3.9	3.9	3.8	3.4	0.15	−0.20	0.10
R. H.	5.0	5.1	5.4	4.8	4.5	4.4	4.6	4.1	−0.05	0.60	0.70
S. B.	5.0	4.3	3.7	3.7	4.2	4.1	3.7	3.9	0.95	0.50	0.85
R. S.	3.6	3.5	3.4	3.7	3.7	3.0	3.7	3.8	0.00	0.20	−0.20
N. S.	4.0	4.1	4.1	3.8	3.8	3.4	4.0	3.6	0.10	0.45	0.25
N. H.	5.4	4.3	4.2	4.2	4.3	2.9	3.4	4.7	0.65	1.25	0.80
H. M.	5.1	4.7	4.4	4.5	4.2	3.5	4.7	4.8	0.45	1.05	0.15
H. R.	3.6	4.2	4.3	4.2	4.9	4.9	4.5	3.2	−0.35	−1.00	0.05
Mean	4.32	4.29	4.11	3.99	4.17	3.80	3.99	3.93	0.26	0.32	0.34
SD	0.80	0.55	0.63	0.48	0.35	0.66	0.49	0.55	0.396	0.672	0.372
SE	0.27	0.18	0.21	0.16	0.12	0.22	0.16	0.18	0.132	0.224	0.124
t									1.97	1.43	2.74
P									NS	NS	<0.05

Liver radioactivity. External counts over the liver and thigh (for background) were made in eight subjects. No attempt was made to quantitate all hepatic radioactivity, but instead constant placement of the probe was attempted so that any relative changes in concentration of hepatic radioactivity could be detected. With this method, important volumetric changes distant from the probe could easily have been missed. The net liver radioactivity was related to simultaneous serum radioactivity and expressed as liters of the T4 volume "seen" by the liver probe. The average figures are presented as the lower curve in Fig. 4. No consistent change in hepatic radioactivity appears to have occurred with epinephrine administration.

Serum stable T4-I. Serum stable T4-I concentration was not markedly affected by epinephrine administration (Table III). However, it gradually decreased in most subjects throughout the experiment, and the postcontrol values were significantly lower than were precontrol values despite considerable fluctuation in the measurements.

T4 degradation rate. After conversion of stable T4-I values to T4 equivalent, they were multiplied by volume of distribution and the "day-by-day *k*" to achieve an estimate of the actual daily T4 degradation rate. This value averaged 127 μg on precontrol day 1; 72 μg on precontrol day 4; 61, 44, 67, and 60 μg successively on the 4 days of epinephrine administration; 82 μg on postcontrol day 1; and 90 μg on postcontrol day 4.

Serum T4-binding proteins. Saturation capacities for T4 of T4-binding globulin (TBG) and T4-binding prealbumin (TBPA) are presented in Fig. 5. TBG capacity increased approximately 14% with epinephrine, but this increase was not maximal until the 3rd day and lasted through the 1st postcontrol day. A reciprocal 9% decrease in the TBPA capacity occurred. Studies in sera enriched only with radio-T4 (containing 2 μg/100 ml of stable T4) showed changes in the relative distribution of radio-T4 in the TBG and TBPA fractions corresponding to the changes observed in saturation capacities.

Free T4-I. Fig. 6 shows the changes in free T4-I as determined from the product of the dialyzable fraction and the stable circulating T4-I levels. As both of these determinations are subject to considerable measurement error, the standard deviation of this compound function was quite high. Nevertheless, it was significantly reduced on epinephrine day 4 and postcontrol day 1.
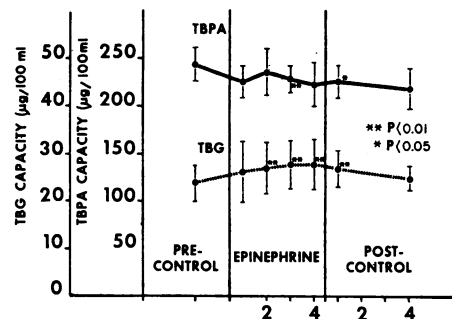

FIGURE 5 Thyroxine-binding globulin (TBG) capacity and thyroxine-binding prealbumin (TBPA) capacity (from sera enriched with 150 and 600 μg/100 ml, respectively, of stable T4). Points and vertical lines indicate means ± standard deviation for the individual subjects. Asterisks indicate significant changes from control figures.
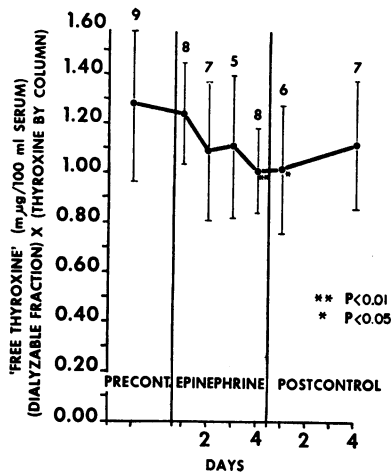
FIGURE 6 Serum free T4. Means ± standard deviation. Numbers indicate number of subjects; asterisks indicate significant changes from control figures.

T3 resin uptake. Fig. 7 shows the results of the T3 resin uptake test performed on sera from the various periods of the experiment. As is the case with TBG capacity and free T4-I, the epinephrine effect on the T3 test was delayed, with significant decreases (corresponding to increased binding by TBG) on days 2–4 of epinephrine administration.

Temporal relationships of the changes in T4 metabolism associated with epinephrine administration. In Fig. 8, day-by-day serum T4 disappearance rate (k), urinary clearance, serum free T4-I, and the inverse of the TBG capacity are presented on scales designed to permit direct intercomparison of their changes with time. As
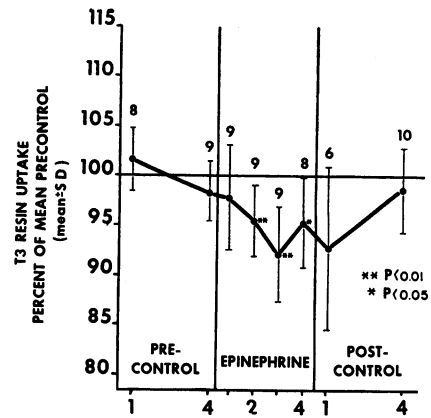

FIGURE 7 Triiodothyronine (T3) resin uptake, mean ± standard deviation, expressed as per cent of the individual's mean precontrol value. Numbers indicate number of subjects; asterisks indicate significant changes from control figures.

previously shown, the serum "day-by-day k" decreased immediately after epinephrine was begun and returned toward control levels while epinephrine administration was continued. The free T4-I and the inverse of TBG capacity decreased slowly during the epinephrine period. When epinephrine was stopped, serum k increased above control levels, while the free T4-I and the inverse of TBG capacity remained depressed through the 1st postcontrol day. Urinary "clearance" changed roughly in parallel with the alterations in free T4-I, suggesting that increased serum T4 binding is responsible for the decreased urinary "clearance" seen late in the period of epinephrine administration. The curve for urinary "clearance" is slightly elevated above the "free T4-I"
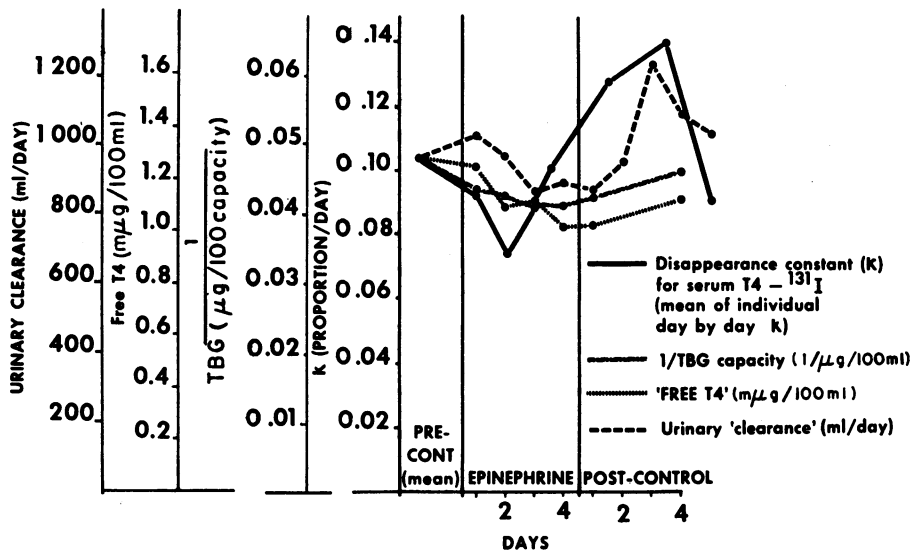

FIGURE 8 Serum "day-by-day k," inverse of TBG capacity, free T4-I, and urinary clearance, plotted on comparable scales.
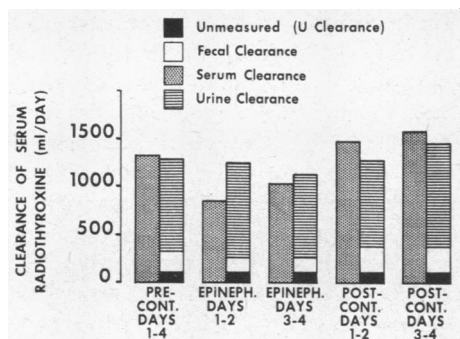
FIGURE 9 Comparison of mean serum clearance ("day-by-day *k*" × volume of distribution) with mean urinary, fecal, and unmeasured clearances during the various experimental periods.

and 1/TBG curves, suggesting the possibility that, when serum binding alterations are allowed for, urinary "clearance" may be *slightly* increased by epinephrine. (This change could well be a random finding. Certainly our data are not sufficient to establish its significance. It is mentioned only because of its correlation with the marked increase in urinary T4 "clearance" noted in the epinephrine-treated rat.)

Fig. 9 presents all of the measurable clearance data (including the unmeasured "U clearance" calculated from the slope of the control volume of distribution curve), for comparison of disappearance from the serum with distribution of the "cleared" radioactivity. Serum clearance values are the product of the "day-by-day *k*" with the volume of distribution for that day. Wide individual random fluctuations are reduced by averaging all individual values and pooling data from successive days and from the 4 precontrol days. Urinary clearances presented are also 2-day means of individual day-by-day measurement. The fecal clearances shown, however, are the mean daily clearances for the entire period of the experiment (precontrol, epinephrine, or postcontrol). Fig. 9 presents a paradoxical picture: during the precontrol period, serum clearance of radioactivity was well accounted for by the excretory clearance measurements. During the 1st 2 days of epinephrine, however, *more* disposition of radioactivity can be accounted for than would have been expected from analysis of the serum data alone. The reverse situation was seen during the postcontrol period: more radioactivity appears to have left the serum than could be accounted for. On epinephrine days 3 and 4, the reduced serum clearance was balanced by reduced urinary clearance. Similarly, by postcontrol days 3 and 4, urinary clearance had increased sufficiently to begin to balance the serum clearance. A possible explanation for the imbalance noted shortly after initiation and after discontinuance of epinephrine will be presented in the Discussion.

DISCUSSION

The decrease in T4 disappearance rate which we have demonstrated (Figs. 1–3) after epinephrine administration in man was quite unexpected. Three separate studies (2–4), using different methodologic approaches, have shown contrary results in the rat. Eskelson, Firschein, and Jensen (2) demonstrated increased serum radio-T4 disappearance after epinephrine was given to rats with endogenously produced serum thyroxine-^{131}I. Kallman and Starr (3) and Galton (4) showed increased urinary radioiodine excretion in animals given synthetic radio-T4 and later given epinephrine. Galton also showed that reserpine decreased urinary radioiodine excretion in the rat and decreased liver deiodination rate in the mouse. Kallman and Starr showed that fecal radioactivity was decreased after epinephrine, a finding compatible with our study. However, despite the great quantitative importance of the hepatoenteric T4 pool in the rat, this fecal conservation was not sufficient completely to account for the increased urinary radioiodine.

In our study, urinary radioiodine excretion may be taken as almost the equivalent of deiodination rate, as thyroidal uptake was blocked by Lugol's Solution. Our findings in man indicate that the deiodination rate of radio-T4 is little if at all affected directly by epinephrine administration. Rather, it parallels closely the serum "free T4-I" level, depending largely upon the capacities of the serum T4-binding proteins. As serum T4 binding in the rat is quite different from that of man, species differences in the response of the deiodination rate to epinephrine could be due to these differences, at least in part. The brief increase in urinary "clearance" several days after epinephrine was stopped remains unexplained. It might indicate a rebound increase in renal iodide clearance rather than increased T4 deiodination.

The decreased free T4-I, resulting presumably from increased TBG production during epinephrine administration, may serve to counteract, to some extent, the physiologic effects of the epinephrine. This could be of clinical importance in view of the well known effects of changes in thyroid hormone levels on response to epinephrine. Our subjects became less uncomfortable toward the end of the 4 day course of epinephrine, perhaps because of this phenomenon.

The disparity noted in the balance bar graphs of Fig. 9 between clearance by each accountable route of excretion of radio-T4 and the apparent total clearance from serum can only be explained by a compartmental shift into the serum, at initiation of epinephrine administration, of radio-T4 from an extravascular tissue compartment which ordinarily binds T4 but does not participate in deiodination. If the amount of T4 bound to such tissue sites decreased when epinephrine administration was begun, this would result in a temporary influx of radio-

T4 into the serum, which would continue until a new steady-state distribution of T4 occurred as epinephrine administration was continued. This influx would have the effect of temporarily reducing the *net* serum T4 disappearance rate even if the actual efflux from the serum were unaltered. Such a mechanism would account for the paradoxical situation seen in Fig. 9 for epinephrine days 1 and 2. The opposite mechanism would be expected immediately after epinephrine was discontinued: exit of serum radio-T4 to resaturate the tissue compartment would temporarily increase the serum clearance, causing it to be greater than the measurable clearances into excreta, as seen in Fig. 9.

Alterations in the disappearance rate of serum T4 due primarily to changes in the tissue T4 compartment have been postulated by Oppenheimer, Bernstein, and Hasen (12). Lutz, Hornick, Dawkins, and Gregerman (13) have shown, in acute febrile illness, that increase in T4 disappearance rate and increase in free T4 often do not occur in the same patient. Braverman, Dawber, and Ingbar (14), in studying effects of aging, show that free T4 remains unchanged despite the known decrease in T4 disappearance rate with age. Alterations in tissue hormone metabolism are suggested as the cause for this change. These studies are at variance with the concept that serum T4 binding, and the free T4 in the serum are the sole determinants of T4 disappearance rate (e.g. see reference 15).

While the data argue strongly in favor of a shift of tissue radio-T4 into the vascular bed when epinephrine is given, the source of this tissue hormone is not established. Even though external counting over the liver is only a crude method, some decrease in liver counts would be expected if the liver were the major source of this influx. Also, the liver is a major site for T4 deiodination (16). Were the liver markedly depleted of radio-T4, a decrease in deiodination soon after epinephrine had been started would have been expected. As this did not occur, extrahepatic tissues, which may account for as much as 34% of the nonthyroidal T4 pool (17) and which might well undergo a reduction in T4 space when epinephrine is given, are the more likely source of this influx.

Epinephrine has many physiological effects, and it is conceivable that the decreased T4 disappearance rate could have been mediated by one of these. However, elevation of basal metabolic rate and increase in free fatty acids, two of the known effects of epinephrine, would if anything have been expected to result in *increased* T4 disappearance rate (18–20). Other effects of epinephrine, such as elevation of blood sugar and lactate and the direct cardiac effects, have themselves no known action on T4 metabolism. Epinephrine does cause profound changes in the blood flow to various

tissues. These changes probably contributed at least in part to the observed shifts in tissue radio-T4 distribution demonstrated in this study. It is also possible that epinephrine can alter the binding affinities of various tissues for T4, so that these tissues compete less effectively with serum proteins for available T4 molecules.

Two apparent difficulties in the data require comment. Firstly, the k values for the precontrol and postcontrol periods calculated from serum radio-T4 regression lines (Fig. 1 and Table I) are somewhat higher than those usually reported (10). Day-by-day k values (Fig. 2) were high early in the precontrol period because of slow equilibration of the dose and early in the postcontrol period in response to epinephrine withdrawal. As the regression line calculations incorporate data from these periods of disequilibrium, the resulting k values are higher than expected.

Secondly, stable serum T4-I levels were lower at the end of the experiment than during the precontrol period (Table III). This finding suggests that thyroidal release of nonlabeled thyroid hormone may have been decreased during the experiment. Two likely causes for such a decrease come to mind: the iodine administered to prevent recirculation of radioiodine by the thyroid, and epinephrine itself. Because of the large hormone pool, a reduced secretion rate due to either cause would not be clearly seen for a number of days. Greer and de Groot (21), using epithyroidal counting, were unable to show any effect of iodine on thyroidal release in normal subjects. This question needs to be reexamined by more sensitive methods, however. As for the effects of epinephrine on thyroidal hormone secretion in man, no studies have come to our attention. Animal studies, employing direct sampling of thyroidal vein blood, show epinephrine to increase (22) or not to affect (23, 24) thyroidal hormone secretion rate. In any case, in the present study the decline in serum T4 concentration was progressive, continuing during the postcontrol period, and therefore is not easily attributable to an epinephrine effect.

Returning to the analysis of the observed decrease in serum radio-T4 disappearance rate due to epinephrine, we have considered the following hypotheses: (*a*) Decreased deiodination of T4 (resulting directly from the effect of epinephrine); (*b*) Increased volume of distribution, (so that, for a given deiodination rate, the fractional [but not absolute] disappearance per liter would be less); (*c*) Influx of stable T4 from increased thyroidal secretion. This would decrease the specific activity of the circulating radio-T4, followed by a decrease in the fractional disappearance rate; (*d*) Decreased distribution to and (or) binding by nondeiodinating tissue sites. This would tend to increase serum radio-T4 levels or to decrease the net disappearance

rate; (e) Increased serum T4 binding with resultant decrease in free T4 available for deiodination; (f) Decreased excretion through the hepatoenteric route.

This experiment shows the first three of these hypotheses (a–c) to be false; (d) appears to be theoretically plausible, and (e) and (f) have been demonstrated to occur. We conclude, then, that epinephrine causes a decreased fecal excretion of radio-T4 and an increased TBG binding capacity which results in a lowered free T4-I level by the 3rd day of continued epinephrine administration. Finally, and quantitatively most important, epinephrine causes an acute shift of tissue radio-T4 stores into the vascular compartment.

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